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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/633,093	08/04/2000	Joel S. Greenberger	07787-004003	2079

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	21

DATE MAILED: 09/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/633,093	GREENBERGER ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 21-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 21-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *20* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/3/03 has been entered.

The amendment filed with RCE has been entered as Paper No. 19. Currently, claims 1-11 and 21-31 are under examination, claim 31 is newly submitted.

Unless otherwise indicated, previous rejections that have been rendered moot in view of new grounds of rejection will not be reiterated. The arguments in paper #19 would be addressed to the extent that they apply to current rejection.

Previous rejections under § 103 have been modified as shown below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 29, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the means of cryopreserving the transfected BMSCs so that they are able to have a level of expression of the exogenous gene which is at least about 77% of said predetermined value in the thawed state.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-9, 21, 22, 24-26, 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), taken with *Greenberger et al* (EP 0 381 490 A2, 8-8-90), *Boswell et al* (Exp. Hematol 1983), *Emerson et al* (US 6,326,198), *Yamada et al* (Nagoya J Med Sci 1982;44:117-31), *Brinster* (US 5,817,453), *Rowley* (J Hematotherapy 1992;1:233-250), and as evidenced by *Hacker et al* (Proc Am Asso Can Res 1975;16:66).

Applicants did not present new arguments to the reasoning presented in the final and advisory actions, thus, for reasons of record, the rejection stands. However, the

rejection has been modified to specifically address the newly submitted claim 31, but it applies to all the claims listed because they encompass the method and resulting product detailed in claim 31.

Newly submitted claim 31 is drawn to a method of preserving bone marrow stromal cells transfected with an exogenous gene comprising washing, detaching, suspending the transfected BMSCs in a cryopreservation medium containing 10%DMSO, 1-50% FBS, and 40-89% DMEM, and storing the transfected cells at about -80^0C.

Anderson et al teach hematopoietic cells such as lymphocytes could be transfected with an exogenous gene, and cryopreserved for later use, they provide motivation for cryopreservation of genetically modified cells, i.e. to reduce repeated painful procedures for obtaining cells from patients, and efficiently use of the transfected cells.

Greenberger et al teach bone marrow stromal cells could also be used as gene therapy vehicle, i.e. transfected with a foreign gene, and *Greenberger et al* teach that BMSCs may be more efficient in transgene expression than hematopoietic stem cells. (paragraph 4, page 2). Although they did not discuss cryopreservation, it should be noted that cryopreservation is an integrated part of any cell culture procedure of continued cell preservation and at the introduction of any new cell type, thus, it is necessarily present in any cell culture laboratory.

However, neither *Anderson* nor *Greenberger* discuss the details of cryopreservation technique.

Boswell et al teach details of cryopreservation for *both* hematopoietic stem cells and bone marrow stromal cells, the method comprising suspending said cells in a medium comprising 10%DMSO, 20%FBS, and 70% culture medium McCoy's 5A, and the cells were stored at about -90^0C. *Boswell et al* do not teach using DMEM as the medium for cryopreservation.

Emerson et al teach the proper culture medium for hematopoitic stem cells, as well as bone marrow stromal cells, include DMEM, RPMI1640, and McCoy's medium (column 8, lines 37-41, columns 9-10, and 19-20). Apparently, it is well known in the art that both McCoy's 5A and DMEM are equally effective in culturing BMSCs.

Yamada et al teach the method of cryopreservation of peripheral blood lymphoid cells comprising suspending the cells in a medium containing 20%FCS, 20% DMSO, and 60%RPMI 1640, and gradually reach -80^0C to -196^0C. They concluded that the cryopreserved lymphocytes not only have 90-98% viability when tested by the trypan blue dye exclusion but also functionally equivalent when compared to freshly isolated PBL cells. This teaching illustrated general state of the art in cryopreservation of peripheral lymphocytes.

Brinster teaches details of cryopreservation for spermatogonia cells as well as for genetically modified primitive cells (Example C). They teach that donor testis cells isolated from prepubertal or adult animals could be cryopreserved with relatively **standard** preservation techniques, and that the spermatogenesis could be successfully maintained (column 21, lines 46-55). In an illustrated example, they freeze and thaw the male germ cells *transduced* with an exogenous transgene LacZ as a marker for

assessing the spermatogenesis of the cryopreserved male germ cells (column 22, lines 12-52). The illustrated (standard) cryopreservation medium comprising 10% DMSO, 10% FBS, and DMEM (column 25, lines 30-35), and *Brinster* also teaches McCoy's 5A is equally effective medium (column 7, lines 18-20). *Brinster* goes on to teach that this technique is applicable to other mammalian species. Apparently, the medium comprising 10% DMSO, 10% FBS, and DMEM is considered as the standard cryopreservation technique, and it has proven to be able to preserve the genetic information of a germ cell as well as the functionality of a transgene in a transduced cell. The teaching of Brinster provides motivation and practice for cryopreservation of genetically modified cells, and illustrates the general state of the art for cryopreservation.

Rowley teaches the general technique of cryopreservation comprising suspending the cells in a cryopreserving medium containing DMSO, FBS, and appropriate culture medium, and stored at the temperature ranging from -80^0C to -196^0C (see particularly page 238-240, and 242-243), which meets the condition recited in claim 31.

Although not relied upon, *Hacker et al* report assessment of cryopreservation effects on drug-resistance and nucleic acid metabolism of leukemic cells, and concluded that rates of DNA were least effected by freezing. This teaching illustrated the general knowledge of the skill concerning the influence of cryopreservation on DNA, whether it is the endogenous or exogenous origin.

From the teachings of *Boswell et al, Yamada et al*, *Rowley,* and *Brinster,* it is apparent that essentially one standard technique has been used in preserving wide variety of cell types, including stem cells, germ cells, stromal cells, and matured lymphocytes, as well as transfected cells carrying an exogenous gene. *Hacker* reference further evidenced what is known in the art regarding the response of DNA to cryopreservation.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the methods taught by *Boswell et al, Yamada et al*, *Rowley,* and *Brinster* in cryopreserving the cells as taught by *Anderson et al,* and *Greenberger* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for reasons as taught by *Anderson et al and Brinster.* Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

It is further noted that the claim recitation, "*wherein said transfected BMSCs in the thawed state have a level of expression of the exogenous gene which is at least about 77% of said predetermined value*" has not given patentable weight in determining the novelty of the invention, This is because it merely recites an intended level of expression of thawed BMSCs, wherein it seems that the method taught by the cited prior art could achieve the instantly claimed levels of transgene expression by the

standard cryopreservation technique, wherein there is no structural or manipulative difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. **If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).**

Additionally, the court also states, the patent Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist (or that the claimed products are functionally different than those taught by the prior art) and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPBI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922, 1923 (BPAI 1989).

Claims 6, 23, are rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), *Greenberger et al* (EP 0 381 490 A2, 8-8-90), *Boswell et al* (Exp. Hematol 1983), *Emerson et al* (6326198), *Yamada et al*

(Nagoya J Med Sci 1982;44:117-31), *Brinster* (5,817,453), *Rowley* (J Hematotherapy 1992;1:233-250), as applied to claims 1-5, 7-10, 21, 22, 24-26, 29-31 above, and further in view of *Lozier et al* (Hum Gene Ther 1994).

These claims are directed to a method comprising transfecting cultured bone marrow stromal cells with an exogenous gene, and cryopreserving the transfected BMSCs, wherein the BMSCs are obtained from bone marrow or bones of a vertebrate, particularly a canine.

Although *Brinster* teaches that the techniques for preserving human cells could also be used for other mammalian species, the combined teachings of *Anderson, Greenberger et al*, *Boswell et al*, *Emerson et al*, *Yamada et al, Brinster*, *Rowley* as discussed in detail above do not particularly teach a canine model. *Lozier et al* reference is relied upon for the canine model.

Applicants did not present new arguments to this rejection, thus, for reasons of record, the rejection stands.

Claims 10, 11, 27, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Anderson et al* (US 5 399 346, 3-21-1995), *Greenberger et al* (EP 0 381 490 A2, 8-8-90), *Boswell et al* (Exp. Hematol 1983), *Emerson et al* (6326198), *Yamada et al* (Nagoya J Med Sci 1982;44:117-31), *Brinster* (5,817,453), *Rowley* (J Hematotherapy 1992;1:233-250), as applied to claims 1-5, 7-10, 21, 22, 24-26, 29-31 above, and further in view of *Newman et al* (US 6,020,188).

These claims are directed to a method comprising transfecting cultured bone marrow stromal cells with an exogenous gene, and cryopreserving the transfected BMSCs, wherein the exogenous gene encodes an adhesion molecule, such as I-CAM.

The combined teachings of *Anderson, Greenberger et al*, *Boswell et al*, *Emerson et al*, *Yamada et al, Brinster*, and *Rowley* have been discussed in detail above, although *Brinster* teaches that the gene used for transfecting cells for gene therapy includes adhesion molecule (column 9, lines 13-14), they do not particularly recite the type of adhesion molecule or ICAM.

However, before the effective filing date of the instant application, *Newman et al* teach polynucleotides encoding a cell surface adhesion molecule, specifically PECAM-1 (see abstract) and mammalian cells transduced by the polynucleotide (column 8, lines 9-16). *Newman et al* teach that well know CAMs also include N-CAM and ICAM (column 1, lines 48-65), and these molecules could be used for modulating angiogenic process, which depend on neutrophil chemotaxis and interaction with endothelial cells (column 8, lines 51-58).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to simply transducing the cell population of interest with a cell surface molecule such as CAMs and cryopreserving such using the methods taught by *Anderson et al, Greenberger, Boswell et al*, *Emerson et al*, *Yamada et al, Brinster*, and *Rowley*, with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it is within the knowledge of the skill to select a gene of interest for expression in a cell population of interest.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
September 22, 2003